

DISCUSSION OF THE AMENDMENT

The specification and Abstract have each been amended, consistent with the amendment in the parent application.

Claim 13 has been amended, and new Claims 17-28 added, as supported in the specification at page 17, line 1 through page 20, line 22.

No new matter has been added by the above amendment. Claims 13-28 are now pending in the application.

REMARKS

As recited in above-amended Claim 13, the present invention is a method of producing a hyaluronic acid gel which comprises adjusting a hyaluronic acid, or alkali metal salt thereof, solution to a pH 3.5 or below, and freezing and thawing the solution at least once.

The rejections of Claim 13 under:

35 U.S.C. § 102(b) as anticipated by “Synthesis of Polysaccharide Chemical gels by Gamma-Ray Irradiation” (Paparella et al) or U.S. 5,143,724 (Leshchiner et al); and

35 U.S.C. § 102(e) as anticipated by U.S. 5,616,568 (Pouyani et al),  
are respectfully traversed.

Paparella et al discloses, *inter alia*, acidification of a solution of hyaluronic acid functionalized with glycidyl acrylate to pH 3, and then subjecting it to gamma-irradiation to form a gel thereof, followed by air drying and oven drying. However, Paparella et al neither discloses nor suggests the presently-claimed invention, since Paparella et al neither discloses nor suggests freezing and thawing the solution of hyaluronic acid.

Leshchiner et al discloses viscoelastic gel slurries formed from a polymeric gel such as of hyaluronic acid, in an aqueous medium, and a fluid phase which is an aqueous solution which may be, but does not have to be, hyaluronic acid. The Examiner asserts that Leshchiner et al “teaches a method of making a hyaluronic acid gel comprising the acidification and freeze-drying of aqueous hyaluronic acid solution,” relying on the disclosure in Example 3 therein.

In reply, the relied-upon disclosure in Example 3 does not support the Examiner’s finding. In Example 3, hydrochloric acid is added to a gel, not a solution, and moreover, it is added to neutralize an alkali previously added (column 11, line 64 through column 12, line 10). While Leshchiner et al discloses subsequently freeze-drying of the gel (column 12, line

18), the present invention requires, at least for the first freezing and thawing cycle, that the solution, not the gel, be frozen and thawed. In addition, though the Examiner also relies upon Examples 4 to 8 of Leshchiner et al, Examples 4 to 8 are irrelevant because they all relate to determination of the rheological properties of the hyaluronic acid gel.

Pouyani et al discloses hyaluronate functionalized with dihydrazide (HA). Pouyani et al discloses that such functionalization is preferably carried out “under mild conditions including a pH of about 2 to 8 preferably about 3 to 6”, carbodiimide is added, and reaction is allowed to proceed “at a temperature of about 0°C to about 100°C (e.g., just above freezing, 0°C, to just below boiling (100°C)), preferably at or near ambient temperatures for purposes of convenience” (paragraph bridging columns 7 and 8). Pouyani et al characterize the product formed as “viscous or gel-like in aqueous solution at relatively low solute concentrations” (column 8, lines 19-20).

Contrary to the finding by the Examiner, Pouyani et al neither discloses nor otherwise suggests the presently-claimed invention. While Pouyani et al may operate at a pH below 3.5, nevertheless, Pouyani et al neither discloses nor suggests freezing and thawing a solution. Indeed, as described above, Pouyani et al carries out their reaction above the freezing temperature and below the boiling temperature.

The descriptions at column 13, lines 56-67 and at column 15, lines 49-61 of Pouyani et al both relate to the hydrogel prepared by crosslinking the hydrazide-functionalized hyaluronate with a bifunctional crosslinker. In column 17, lines 29-52 of Pouyani et al, a hydrazido-functionalized HA was prepared by reacting HA under an acidic solution, and the product was neutralized and purified by column chromatography and freeze-dried. Thus, again, Pouyani et al neither discloses nor suggests freezing and thawing a solution.

For all the above reasons, it is respectfully requested that the rejections over prior art be withdrawn.

The objection to the Abstract is now moot in view of the above-discussed amendment. Accordingly, it is respectfully requested that it be withdrawn.

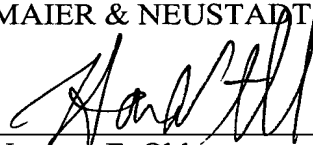
Applicants respectfully call the Examiner's attention to the Information Disclosure Statements (IDSs) filed June 24, 2002 and January 17, 2002. The Examiner is respectfully requested to initial the Forms PTO 1449 submitted therewith, and include a copy thereof with the next Office communication.

Moreover, since the date of both of the IDSs is before the date of the Office Action and thus technically were part of the Official file as of the Office Action date, Applicants respectfully request that should the Examiner determine that a new ground of rejection needs to be made in the next Office Action relying in whole or in part on any of the references cited in the IDSs, then said next Office Action not be made Final, even if the new rejection was necessitated by the present amendment to the claims.

Applicants gratefully acknowledge the Examiner's indication of allowability of Claims 14-16. Nevertheless, Applicants respectfully submit that all of the presently pending claims in this application are now in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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